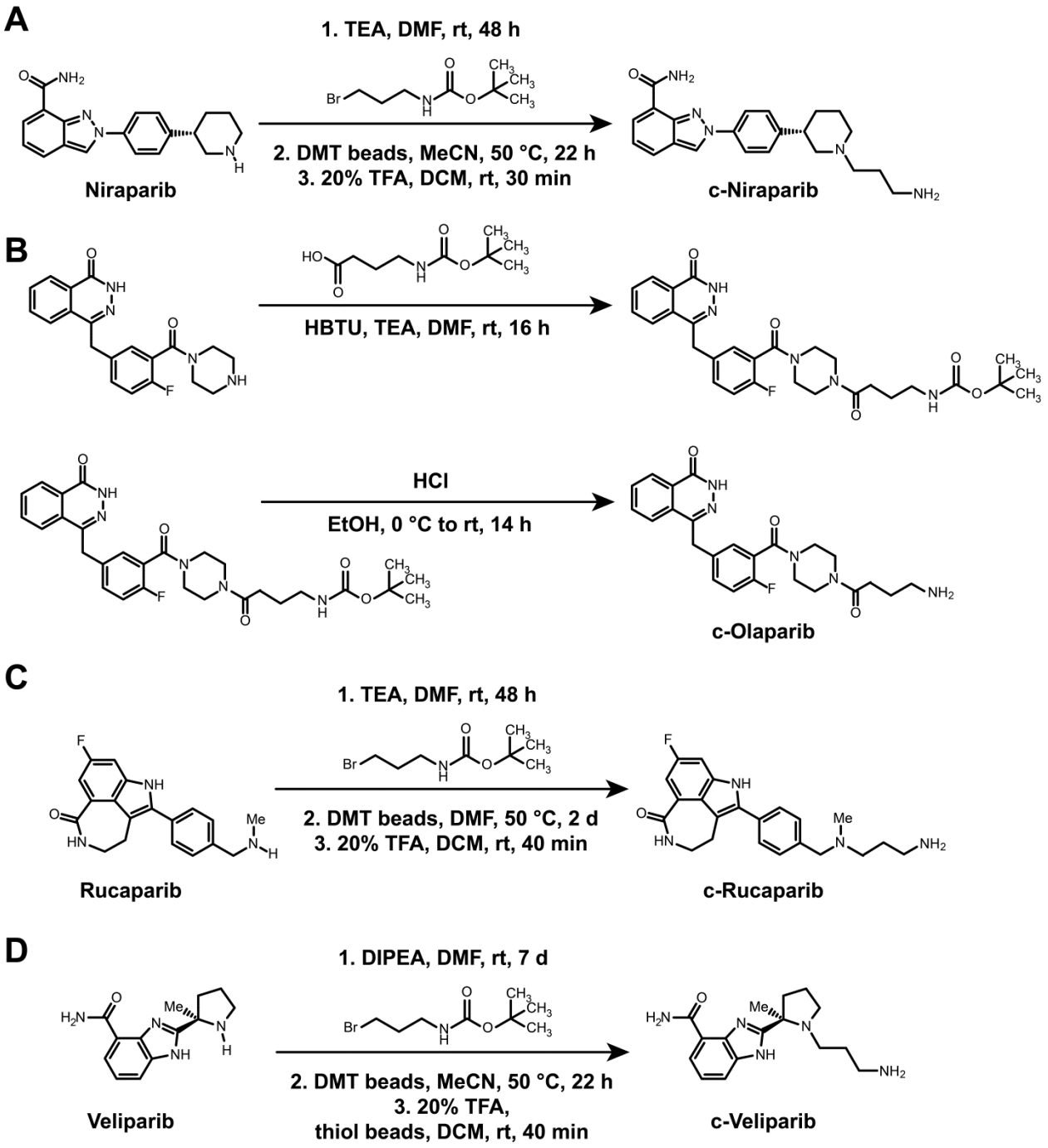



**Figure S1. Synthetic schemes for the preparation of coupleable PARPi – related to Figure 1. (A)** Synthesis of c-niraparib. **(B)** Synthesis of c-olaparib. **(C)** Synthesis of c-rucaparib. **(D)** Synthesis of c-veliparib.

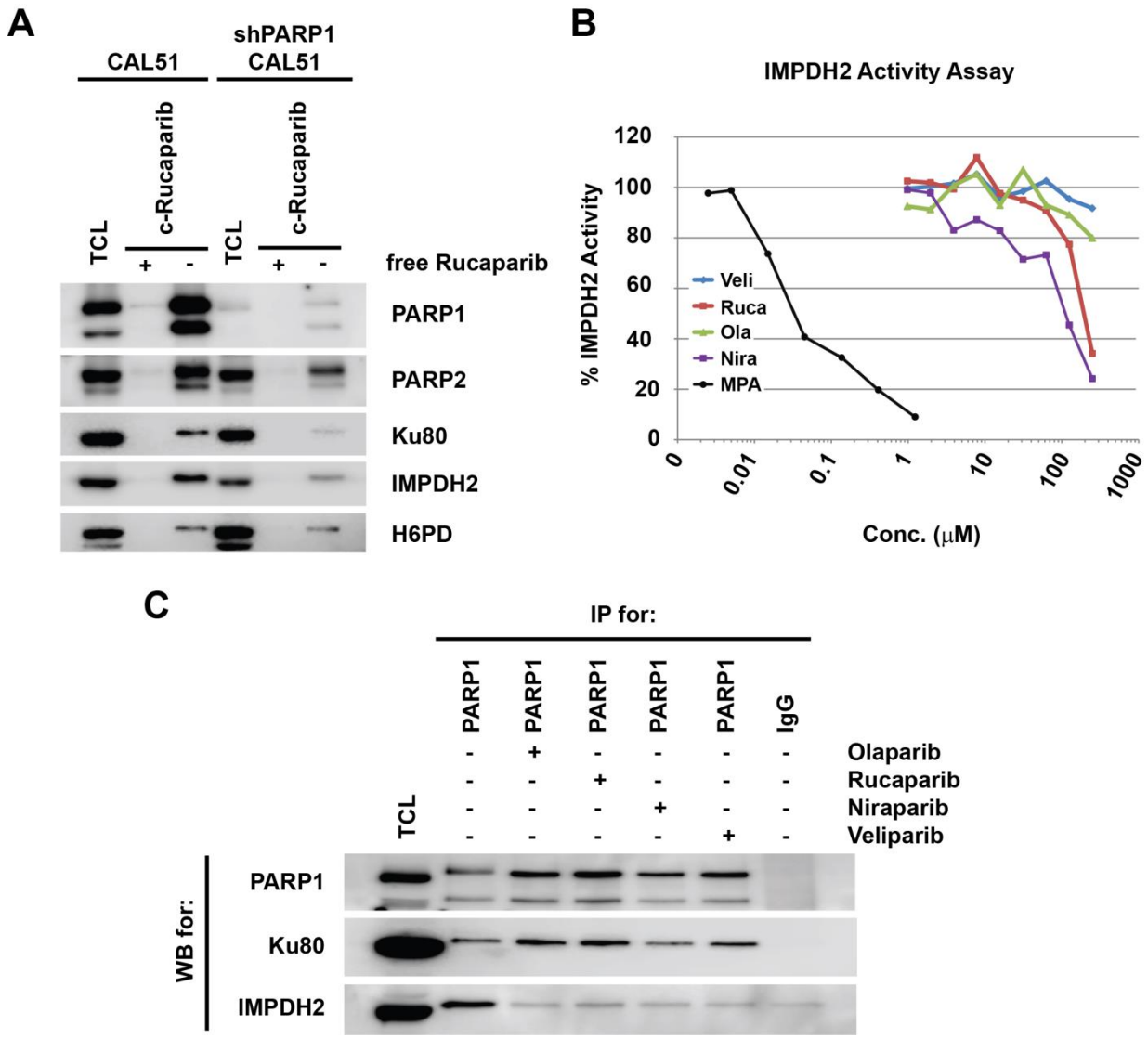



**Figure S2. IMPDH2 binds to PARP1/2 – related to Figure 2. (A)** Immunoblots of eluates from rucaparib-modified beads incubated with CAL-51 or stable shPARP1 CAL-51 lysate ± 20 μM free rucaparib. **(B)** *In vitro* assay of IMPDH2 enzymatic activity in presence of increasing concentrations of olaparib, rucaparib, niraparib, veliparib, or mycophenolic acid (MPA). **(C)** Immunoblots of PARP1 and rabbit IgG immunoprecipitates from CAL-51 cell lysate + 20 μM free PARPi or DMSO. Blots are representative of two independent experiments.

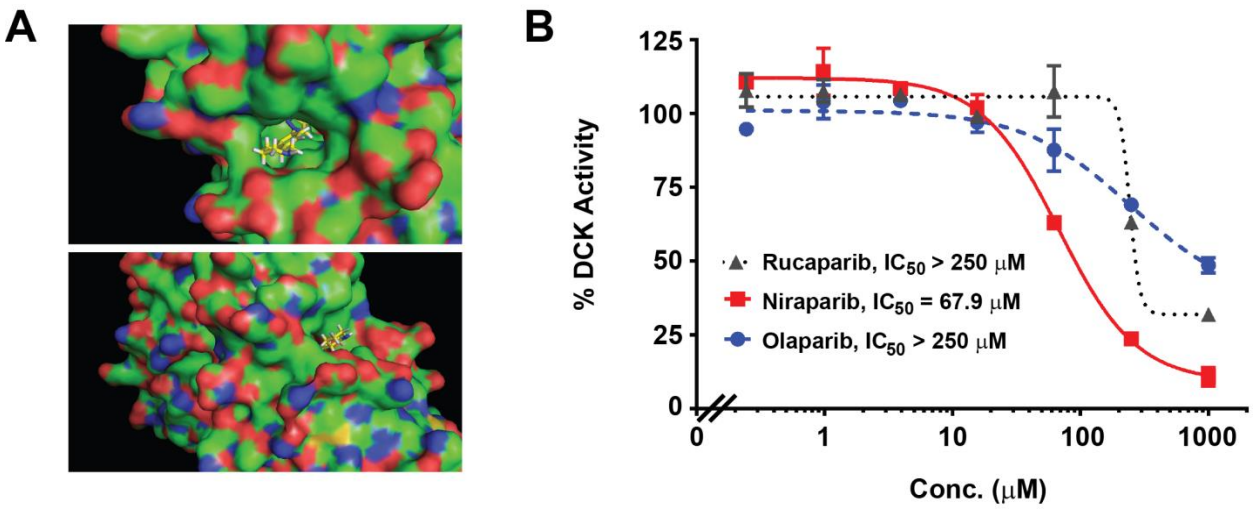



**Figure S3 – related to Figure 4. (A)** Docking of niraparib in the DI-39/substrate pocket of DCK structure 4KCG. Niraparib binds with the piperidine extending outside of the inhibitor pocket; score -9.6. **(B)** DCK activity in cell lysates of CCRF-CEM cells in the presence of increasing concentrations of olaparib, rucaparib, or niraparib as measured by phosphorylation of [$^3$H]-deoxycytidine, n = 2, s.e.m.

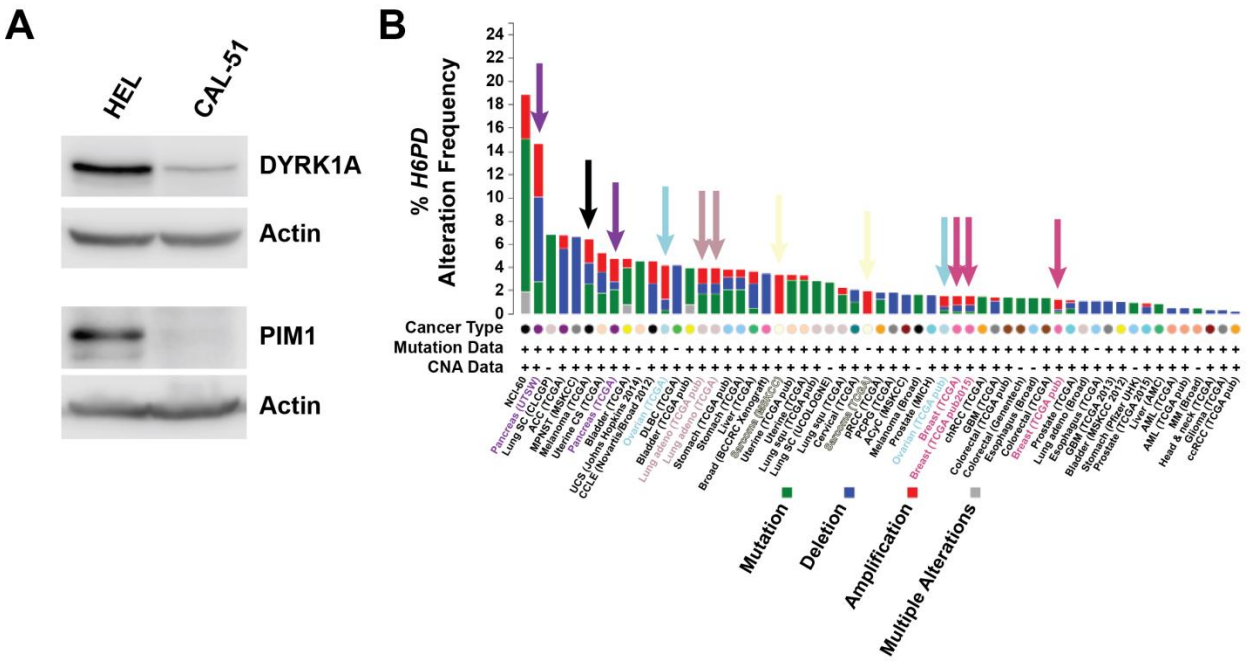



**Figure S4 – related to Figures 3 and 7. (A)** Expression of DYRK1A and PIM1 in CAL-51 cells compared to HEL human erythroid leukemia cells. For DYRK1A 50 µg of protein was loaded, for PIM1 100 µg. **(B)** Somatic alterations of *H6PD* across human cancers. Querying The Cancer Genome Atlas (TCGA) and other publically available data with cBioPortal,[1] *H6PD* is not commonly altered in human tumors, but gene amplification is observed in as much as 3-4% of pancreatic, ovarian and sarcoma tumors, and 1-2% in breast cancer, lung adenocarcinoma and melanoma (indicated by arrows; colors correlate with c-BioPortal cancer type color coding). Of the other types of alterations, most mutations reported are missense and predicted to have no impact on function.

## SUPPLEMENTAL INFORMATION

**Table S1 – related to Figure 2.** Exclusive unique spectra counts for proteins identified in PARPi and competition (denoted by CT) chemical proteomics experiments, including calculations for criterion score analysis. Six different criteria were applied and scores were calculated on a 0 (meet none of the criteria) to 6 (meet all criteria) scale. Criteria were based on the sum of spectra in all three enrichments, the ratio of spectra to protein size, and the ratio of spectra in PARPi enrichments to the spectra in competition experiments.

**Table S2 – related to Figure 2.** NSAF values for proteins identified in PARPi chemical proteomics experiments, calculated using total spectra counts. A subset of this data is represented in Figure 2A.

**Table S3 – related to Figure 2.** Subset of data shown in Table S1 used to generate the interaction network in Figure 2B. Only proteins with a criterion score of 6 for one or more c-PARPi are included.

**Table S4 – related to Figure 3.** SAINTexpress input (prey, total spectra counts, and control counts) and output (SAINT score and fold change) used to prepare graphs in Figure 3.

**Table S5 – related to Figure 3.** Total spectra counts for proteins identified from ampicillin-enrichment of CAL-51 cell lysate. This data was used as control data in SAINTexpress analyses graphed in Figure 3A-D.

## SUPPLEMENTAL EXPERIMENTAL PROCEDURES

### Antibodies and Chemicals

*Antibodies:* PARP1 (Cell Signaling, 9542S), PARP2 (Active Motif, 39743), H6PD (Santa Cruz, sc-377180), DCK (Millipore, MABC188), IMPDH2 (Sigma Aldrich, HPA001400), Ku80 (Santa Cruz, sc-5280), DYRK1A (Cell Signaling, 2771), PIM1 (Santa Cruz, sc-13513), cleaved caspase-3 (Cell Signaling, 9661), beta-actin (Sigma Aldrich, A5441), rabbit IgG (Santa Cruz, sc-2027), ECL Mouse IgG HRP-linked (GE Healthcare, NA931), ECL Rabbit IgG HRP-linked (GE Healthcare, NA934), Protein A-HRP conjugate (Fisher, 32400).

*Chemical compounds:* Veliparib, olaparib, niraparib, rucaparib (all Chemietek) and ampicillin (Sigma Aldrich) were dissolved in DMSO at a concentration of 10 mM and stored at -20 °C. Cytarabine (AraC) and deoxycytidine (dC) were purchased from Sigma Aldrich. DI-39 was prepared as previously reported and stored at -20 °C as a 10 mM stock in DMSO.[2]

### Biology Methods

*PARP1 Activity Assay*

Inhibition of PARP1 was assessed using the Universal Chemiluminescent PARP Kit (Trevigen, 4676-096-K) as directed. Test compounds were diluted in assay buffer yielding a final DMSO concentration of 0.4%. Luminescence readings were normalized to controls and fit to a sigmoidal dose response curve using GraphPad Prism 6 to determine $IC_{50}$ values.

*Cell Culture*

HEK293, HEK293 H6PD-OE and MCF7 were maintained in Eagle's MEM with 10% FBS. CAL-51, CAL-51 shNT, CAL-51 shH6PD and CAL-51 H6PD-OE were maintained in DMEM with 10% FBS. A549, H23, A427, H322, MDA-MB-468 and H1648 were maintained in RPMI1640 with 10% FBS. IPC-298 and M245 were maintained in RPMI1640 with 5% FBS. All preceeding cell lines were maintained at 37 °C in the presence of 5% $CO_2$. MDA-MB-231 were maintained in Leibovitz's L15 with 10% FBS at 37 °C in atmospheric air. Cell pellets of IPC-298 and M245 were a kind gift from Dr. Keiran Smalley. CAL-51 cells were obtained from DSMZ, HEK293, NCI-H23 and A549 cells from ATCC. H1648 were obtained from Dr. John Minna (UT Southwestern) and H322 were obtained from Dr. Paul Bunn (University of Colorado).

*Flow Cytometry*

Cells were stained for flow cytometry with APC Annexin V (BD Biosciences cat# 550474) and DAPI (0.1 μg/ sample; Sigma cat# D9542) according to BD Biosciences APC Annexin V staining protocol. Flow cytometry was performed on a BDFACS CANTOII. Analysis was performed using FLOWJO software.

*Cell Viability Assays*

Cells were seeded (CAL-51: 250 cells/well, H322, MDA-MB-468 and A549: 500 cells/well) into black clear-bottom 384-well plates. After 24 h compound was added (final DMSO concentration of 0.4%). Cells were incubated in a 37 °C 5% $CO_2$ incubator for 5 (CAL-51, H322, MDA-MB-468) or 3 days (A549) prior to analysis with CellTiter-Glo Luminescent reagent (Promega). Plates were read on a M5 Spectramax plate reader (Molecular Devices), cell viability was normalized to vehicle-treated wells and fit to a sigmoidal dose response curve using GraphPad Prism 6. Percent rescue from cytarabine toxicity was calculated by normalizing PARP inhibitor-only treated wells or DI-39-only treated wells as 100% rescue and cytarabine only-treated wells as 0% rescue.

*Cell Lysate Preparation for Proteomics and Co-Immunoprecipitation*

Cells were harvested, pelleted by centrifugation and lysed with an equal volume of lysis buffer (50 mM Tris, 5% glycerol, 1.5 mM $MgCl_2$, 100 mM NaCl, 0.2% NP-40, 25 mM NaF, 1 mM $Na_3VO_4$, 1 mM PMSF, 1 mM DTT, 30 µM TLCK, 30 µM TPCK, 1 µg/mL leupeptin, 1 µg/mL aprotinin, 10 µg/mL trypsin inhibitor, pH 7.5) as described previously.[3] The lysis mixture was centrifuged twice at 21,000xg and 4 °C (10 min, 20 min) and the protein concentration was determined using a Bradford assay.

*Chemical Proteomics*

Experiments were performed essentially as described before.[3] All enrichments were performed three times in independent experiments, except ampicillin enrichments which were performed twice. C-veliparib, c-niraparib, c-rucaparib, c-olaparib, and ampicillin were immobilized on NHS-activated beads and blocked overnight. Lysate (5 mg protein per sample) was pre-incubated with competition compound (20 µM for free PARPi, 1 mM for deoxycytidine, 10 µM for DI-39) or DMSO for 30 min at 4 °C. Affinity pulldown experiments were performed by incubating lysates for 2 h at 4 °C with drug-modified beads. After washing beads with lysis buffer, bound proteins were eluted by heating to 100 °C in Laemmli buffer for 5 min. A portion of each eluate was set aside for analysis by immunoblotting. SDS-PAGE, in-gel digestion with trypsin and LC-MS/MS analyses using a nanoflow liquid chromatograph (Dionex RSLC, Thermo) online with a hybrid LTQ-Orbitrap mass spectrometer (Thermo) were performed as described previously.[4] Data was searched against the SwissProt 2015 human protein database using the Mascot search engine (Matrix Science). Up to two missed cleavages by trypsin were allowed and carbamidomethylation of cysteine and methionine oxidation were selected as variable modifications. Mass tolerance was set to 1.2 to accommodate selection of ion signals other than the monoisotopic peaks and fragment ion tolerance to 0.8 for MS/MS data from the linear ion trap. Results were visualized in Scaffold 4.3.4, (www.proteomesoftware.com), using a protein threshold of 50%, minimum of 1 peptide, and a peptide threshold of 95%. Peptide counts were analyzed as Exclusive Unique Spectrum Count, except where otherwise specified, and proteins were scored based on specificity (competition), relative abundance and reproducibility across replicates as defined in Table S1.

*SAINT Analysis of Chemical Proteomics Data*

Using Scaffold, the total spectra count for all proteins in each sample was exported and bait/inter/prey input files were prepared. For one analysis type, the PARPi affinity purifications were compared against the competition purifications with free PARPi and the ampicillin purifications as control samples. For the other type of analysis, one PARPi purification sample set was compared to the other 3 PARPi purification sets as control samples. These input files were processed using SAINTexpress,[5] and the fold-change and SAINT scores were plotted on a bubble graph, with the bubble size proportional to the Normalized Spectral Abundance Factors (NSAF).[6] The CRAPome probability score, which was used to color the bubbles, was calculated by first searching for each protein in the CRAPome database and then dividing the number of experiments where the protein is detected by the total number of experiments in the CRAPome.[7] Thus, a low CRAPome probability score corresponds to fewer instances identified as a contaminant in the CRAPome, and vice versa for a high score. For proteins that are not contained in the CRAPome database, a probability score of 0 was assigned.

*Immunoblotting*

Total cell lysates (20-50 µg protein) for immunoblotting were prepared as described above, except the lysate was centrifuged only once for 20 min. Some samples were lysed in RIPA buffer (10 mM Tris, 150 mM NaCl, 5 mM EDTA, 1% Triton X-100, 0.1% sodium deoxycholate, 0.1% SDS, 25 mM NaF, 1 mM $Na_3VO_4$, 1 mM PMSF, 1 mM DTT, 30 µM TLCK, 30 µM TPCK, 1 µg/mL leupeptin, 1 µg/mL aprotinin, 10 µg/mL trypsin inhibitor, pH 7.4) following the same procedure. Proteins were resolved in 8-10% polyacrylamide gels and transferred to activated PVDF using the TransBlot Turbo system (BioRad). Membranes were blocked and probed with primary and

secondary antibodies according to standard techniques. Bound antibody was detected with ECL reagents and imaged using either x-ray film or an Odyssey FC Imager (LI-COR). For analysis of chemical proteomics experiments, the volume of the denatured eluent was estimated and 5-10% was loaded on the gel.

*Co-Immunoprecipitation*

50 µL of Protein A/G beads were rotated overnight at 4 °C with 2 µL PARP-1 antibody, PARP-2 antibody or rabbit IgG antibody. Beads were washed 3x with lysis buffer (without DTT) before addition of cell lysate (1.4 mg) and rotated at 4 °C for 4 h. When DMSO or PARPi were used, these were added to cell lysate immediately before incubation with beads. Beads were washed 4 times with lysis buffer and proteins were heat-denatured in presence of 20 µL of 2X Laemmli buffer. For western blot analysis, beads were pelleted by centrifugation (1 min, 10,000xg) and the supernatant (30 µL) was loaded. For detection of IMPDH2 and PARP2, after primary antibody incubation, Protein A-HRP conjugate (1:50,000) was used in place of secondary antibody.

*IMPDH2 Activity Assay*

IMPDH2 activity was assayed by NovoCIB (Lyon, France) at 25 °C in the presence of inosine monophosphate and NAD. Absorbance was monitored at 340 nm for 30 min. MPA: mycophenolic acid.

*H6PD Activity Assay*

HEK293 H6PD-OE and HEK293 (WT) pellets were lysed in 0.1 M Tris pH 7.4, 0.1 M KCl, 1 mM EDTA pH 8.0, 1 mM PMSF. Reaction mix (0.2 mM Galactose-6-phosphate (Gal6P), 0.1 M glycine-NaOH buffer pH 10, 0.5 mM NADP, 1% BSA) was combined with increasing concentrations of PARPi or DMSO. As an additional control, reaction mix without substrate (Gal6P) was combined with H6PD overexpression lysate ($act^{H6PD\text{-}Gal6P}$). Lysate (10 µg/well) from HEK293 or HEK293 H6PD-OE was added to each well to start the reactions ($act^{H6PD+Drug}$, $act^{H6PD+DMSO}$, $act^{wt+drug}$ and $act^{wt+DMSO}$). The absorbance at 340 nm (NADPH) was measured on a SpectraMax M5-plate reader for 90 min at 10 min intervals. The 60 min data, which was within the linear range, was used for analysis. The background absorbance of $act^{H6PD\text{-}Gal6P}$ was subtracted. Since HEK293 (WT) does not have measurable H6PD activity, the difference between $act^{wt+drug}$ and $act^{wt+DMSO}$ was used to calculate drug absorption at 340 nm. H6PD activity in PARPi-containing wells was calculated using the following formula:

$$\text{H6PD activity} = (act^{H6PD+drug\ or\ DMSO} - act^{H6PD\text{-}Gal6P}) - (act^{wt+drug} - act^{wt+DMSO})$$

The H6PD activity of the HEK293 H6PD-OE lysates treated with PARPi was normalized to the DMSO control. Graphs were created in GraphPad Prism 6 using sigmoidal dose response (variable slope), n=5.

*Virus Constructs and Viral Particle Preparation*

Human *H6PD* (Origene, sc117481 XL6) was cloned (XbaI-NotI frgmt) into entry vector pENTR1A (Addgene, 17398) and recombined into destination vector pLenti-CMV-puro (Addgene, 17452) using Gateway LR Clonase II Enzyme mix (Invitrogen-Life Technologies). The resulting construct pLenti-CMV-H6PDshort 3'UTR contains approximately 0.6 kb of the original 3'UTR. Lentiviral constructs containing non-mammalian non-targeting shRNA control (shNT, SHC202), human shH6PD4374 (recognized site 4374 in the 3'UTR of NM_004285.3, Broad Institute Clone ID TRCN0000234333) or human shPARP1-2727 (recognizes site 2727 in the coding sequence of NM_001618.3, Broad instate Clone ID TRCN0000338406) in lentiviral vector TRC2 pLKO were obtained from Sigma.

Virus was prepared by transfection of the constructs together with 3rd generation packaging mix vectors (abm, LV053) into HEK293T using jetPRIME transfection reagent (Polyplus Transfection, 114-15). Fresh media was applied 24 h post transfection. Media was collected 48 and 72 h post transfection. The virus was concentrated (2 h, 72000xg ultra-centrifuge, 4 °C), resuspended overnight in RPMI without serum, aliquoted and stored at -80 °C. Virus was titered using a qPCR Lenti-viral titering kit (abm, LV900).

*Transient and Stable Knockdown and Overexpression*

For transient or stable gene knockdowns, cells were transduced mock (10 µg/mL polybrene), with shNT or human shH6PD4374 virus. For overexpression, HEK293 and CAL-51 were transduced with the pLenti-CMV-H6PDshort 3'UTR virus. Virus and polybrene (10 µg/mL) were removed after 24 h, at which time drug treatment was started or selection for stable lines was initiated with 1 µg/mL puromycin.

Human *H6PD* SMARTpool siRNA (Dharmacon, L-004692-01-0005) and non-targeting control siRNA (Dharmacon, D-001810-10-20) were transfected into CAL-51, H322, or MDA-MB-468 cells in 6-well plates using

Lipofectamine RNAiMAX (Invitrogen) according to manufacturers' instructions for reverse transfection. Cells were seeded at $0.8x10^6$/well for 48 h and $0.4x10^6$/well for 72 h. At 48 and 72 h post transfection, supernatant (sn) was collected, cells were trypsinized and added to sn. Samples were counted for viability or prepared for analysis by flow cytometry.

*DCK Activity Assay*

To determine the $IC_{50}$'s of PARPi for DCK activity, *in vitro* kinase assays were performed as previously described with slight modifications.[8] Briefly, cellular protein was isolated from CCRF-CEM cells (ATCC) by multiple freeze/thaw cycles. Whole cell lysates (1.64 µg) were incubated with 0.2 µCi of $^3$H-labeled deoxycytidine ([$^3$H]deoxycytidine, MT673E, Moravek Biochemicals) in the presence of varying concentrations (0-500 µM) of rucaparib, olaparib or niraparib,. Reactions were performed in duplicate at 37 ºC with 50 mM Tris-HCl (pH 7.6); 5 mM uridine triphosphate; 5 mM $MgCl_2$; 2 mM DTT; 10 mM NaF; 1 mM thymidine. After 30 minutes, the reactions were stopped by adding ice-cold water. The phosphorylated products were selectively bound to Whatman Grade DE81 ion exchange cellulose chromatography paper (GE Healthcare Whatman). After washing out unphosphorylated probes, radioactivity was measured using a beta-counter (Perkin-Elmer).

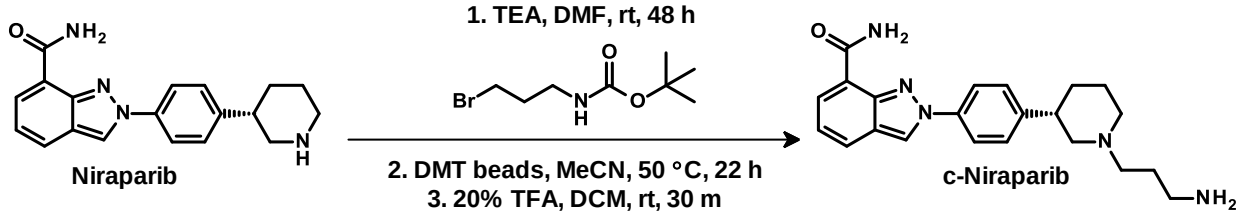
*DCK Docking*

Docking was carried out using AutoDock Vina[9] through the Mcule 1-Click Docking webtool (https://mcule.com/apps/1-click-docking/). Niraparib was uploaded as the following SMILES string: Niraparib: NC(=O)c1cccc2cn(nc12)c3ccc(cc3)[C@@H]4CCCNC4

DCK crystal structure 4KCG[2] was uploaded from the Protein DataBank into Mcule and the nitrogen of the side-chain of GLN97 was chosen as the binding site center, as this side-chain forms the back of the DI-39 binding pocket. Docking was executed using default AutoDock Vina settings and up to 4 top-scoring poses were viewed.

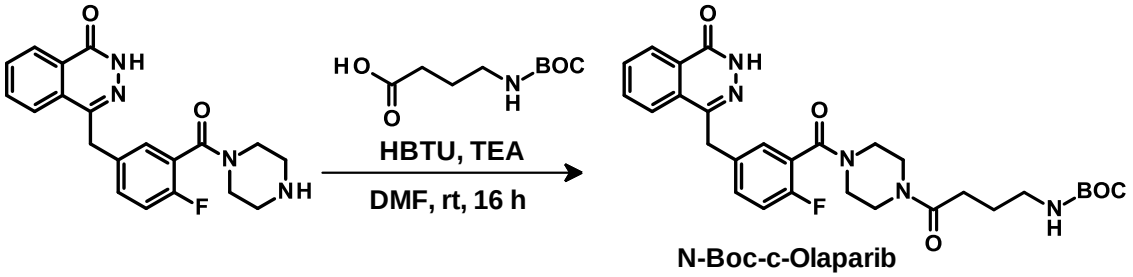
**Chemistry Methods**

**Synthesis of c-Niraparib**

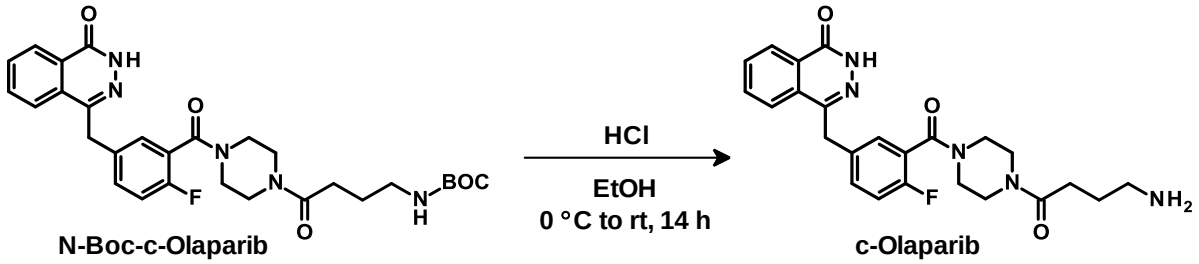



To a 4 mL Teflon-capped vial was added niraparib (9.0 mg, 25 µmol, 1.0 equiv.), *N*-(tert-butoxycarbonyl)-3-bromopropylamine (24 mg, 100 µmol, 4.0 equiv.), $Et_3N$ (13.9 µL, 100 µmol, 4.0 equiv.) in 600 µL DMF. The reaction was stirred at room temperature for 48 h, dried *in vacuo*, and the residue was re-dissolved in MeCN (2 mL). To this solution were added SiliaMetS Dimercaptotriazine beads (500 mg, 300 µmol, 12.0 equiv.) (Silicycle, R79030B, 40-63 µm, 0.59 mmol/g). This mixture was stirred at 50 °C for 22 h, then filtered using Celite with MeOH. The filtrate was concentrated *in vacuo*, dissolved in EtOAc and washed first with $NaHCO_3$ (0.1 M), then with sat. NaCl. The combined organic layer was analyzed by LC-MS to confirm the presence of BOC-protected c-niraparib. This crude product was dried *in vacuo* and used without further purification. Next, the product was dissolved in DCM with 20% TFA, stirred at room temperature for 30 min and dried *in vacuo* yielding a slightly yellow oily residue as c-niraparib•2TFA (13.4 mg, 89% overall yield). HRMS (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{27}N_5O$, 378.22884; found, 378.22854. $^1$H NMR (400 MHz, $d_6$-DMSO): δ 8.99 (s, 1H), 8.15 (dd, *J* = 1.0, 7.0 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 2H), 8.02 (dd, *J* = 1.0, 8.5 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.26 (dd, *J* = 7.0, 8.5 Hz, 1H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.26-3.09 (m, 4H), 3.05 (t, *J* = 6.0 Hz, 2H), 2.22-1.82 (m, 7H). $^{13}$C NMR (100 MHz, $d_6$-DMSO): δ 169.50, 147.96, 142.35, 140.50, 131.68, 129.74, 127.17, 125.28, 124.08, 123.15, 122.24, 121.86, 58.52, 55.39, 53.85, 41.56, 37.86, 30.26, 24.32, 23.38.

**Synthesis of c-Olaparib**

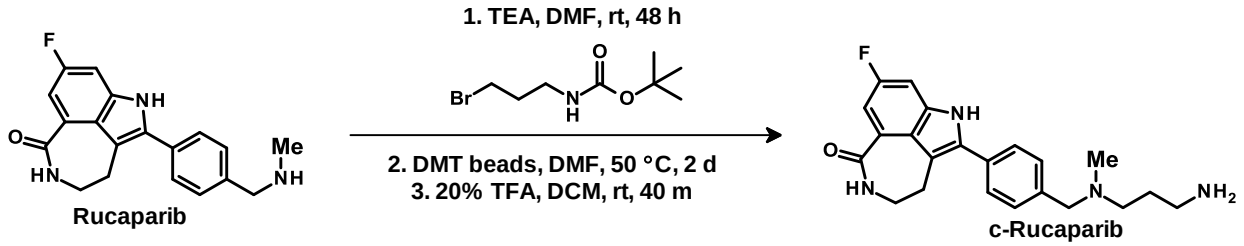



***tert*-Butyl (4-(4-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoyl)piperazin-1-yl)-4-oxobutyl)-carbamate (N-BOC-c-olaparib):** A mixture of 4-(4-fluoro-3-(piperazine-1-carbonyl)benzyl)phthalazin-1(2H)-one[10] (0.250 g, 0.683 mmol), HBTU (0.311 g, 0.820 mmol), BOC-carbonylaminobutyric acid (0.167 g, 0.820 mmol) and TEA (0.190 mL, 0.820 mmol) in DMF (1.5 mL) was stirred at room temperature for 16 h. The reaction was monitored using HPLC-MS, which indicated the completion of the reaction. The crude mixture was diluted with DCM (25 mL) and washed with water (10 mL x 6). The organic layer was dried over $Na_2SO_4$, filtered and concentrated to dryness. The crude material was purified by flash $SiO_2$ chromatography (gradient 0-5% MeOH in DCM) to obtain N-BOC-c-olaparib as a white foaming solid (312 mg, 83%). HRMS (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{29}H_{35}FN_5O_5$, 552.2617; found 552.2601. $^1$H NMR (400 MHz, $d_6$-DMSO): δ 12.59 (s, 1H disappear on $D_2O$ shake), 8.24 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.88 (t, *J* = 7.2 Hz, 1H), 7.82 (t, *J* = 7.2 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.34 (brs, 1H), 7.22 (t, *J* = 9.2 Hz, 1H), 6.81 (appq, 1H disappear on $D_2O$ shake), 4.31 (s, 2H), 3.61-3.48 (m, 4H), 3.16-3.12 (m, 2H), 2.91-2.88 (m, 2H), 2.31 (t, *J* = 6.8 Hz, 1H), 2.24 (t, *J* = 6.8 Hz, 1H), 1.60-1.55 (m, 2H), 1.35 and 1.32 (2 x s, 9H, rotamers); $^{19}$F NMR (376 MHz, DMSO-$d_6$): δ -119.77-119.82 (m); LC-MS (ESI+) *m/z* 452.2 $(M\text{-Boc}+H)^+$.



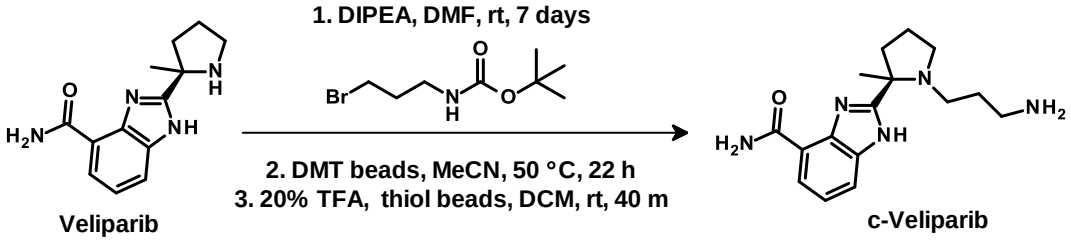

**4-(3-(4-(4-Aminobutanoyl)piperazine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2H)-one (c-olaparib):** To a solution of **N-Boc-c-olaparib** (0.220 g, 0.399 mmol) in EtOH (2 mL) was added aq. HCl (6 M, 4 mL) on an ice bath. After addition of HCl, the mixture was warmed to r.t. and stirred for 14 h. The HPLC-MS indicated 80% of desired product and 20% of 4-(4-fluoro-3-(piperazine-1-carbonyl)benzyl)phthalazin-1(2H)-one byproduct. The EtOH was removed by evaporation and sat. $NaHCO_3$ was added to adjust the pH to 10. The aqueous solution was extracted using DCM (25 mL x 2). The HPLC-MS indicated 80% byproduct in organic phase. The aqueous phase contained 93% pure desired product. The aqueous phase was concentrated to dryness. MeOH (5 mL x 3) was added to the mixture and sonicated; the solid was filtered (inorganic salt). The filtrate was collected and concentrated. MeOH (2 mL x 3) was added again to remove the inorganic salt. This process was repeated with MeOH/DCM (2:8 ratio, 2 mL x 3), then repeated with DCM (3 mL x 3) in order to remove all the inorganic salt. The desired product (0.125 g, 69%) was obtained with 93% purity by HPLC-MS. The product was further purified by dissolving in water (10 mL) and extracting with DCM (10 mL x 2). The aqueous layer was concentrated and dried under high vacuum to afford c-olaparib as a white solid with 97% purity by HPLC-MS (60 mg). LC-MS (ESI+) *m/z* 452.2 $(M+H)^+$; HRMS (ESI+) *m/z* calcd. for $C_{24}H_{27}FN_5O_3$ $(M+H)^+$ 452.2092, found 452.2083. $^1$H NMR (400 MHz, $d_6$-DMSO): δ 8.24 (d, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.88 (appt, *J* = 8.0 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.42 (brt, 1H), 7.34 (appt, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 9.2 Hz, 1H), 4.31 (s, 2H), 3.61-3.12 (m, 8H, overlapped with the water signal at 3.33), 2.61-2.56 (m, 2H), 2.40-2.30 (m, 2H), 1.62-1.57 (m, 2H); $^{19}$F NMR (376 MHz, DMSO-$d_6$): δ -119.77-119.79 (m); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 171.03, 164.45 (d, *J* = 6.2 Hz), 159.83, 156.78 (d, *J* = 243 Hz), 145.32, 135.27, 133.97 (d, *J* = 4.1 Hz), 132.21 (d, *J* = 7.4 Hz), 132.03, 129.49, 129.36 (d, *J* = 3.7 Hz), 128.29, 126.50, 125.92, 123.98 (d, *J* = 13.9 Hz), 116.38 (d, *J* = 21.0 Hz), 46.90 (d, *J* = 33.8 Hz), 45.12 (d, *J* = 44.4 Hz), 41.86 (d, *J* = 33.8 Hz), 41.29 (d, *J* = 55.5 Hz), 36.86, 30.09, 26.46.

**Synthesis of c-Rucaparib**




To a 4 mL vial was added rucaparib (2.8 mg, 8.7 µmol, 1.0 equiv.), *N*-(tert-butoxycarbonyl)-3-bromopropylamine (8.2 mg, 34.6 µmol, 4 equiv.), and $Et_3N$ (2.4 µL, 33 µmol, 3.8 equiv.) in 115 µL DMF. The reaction was stirred at room temperature for 24 h. LC-MS analysis revealed partial conversion to desired product, so an additional 2 equiv. of *N*-(tert-butoxycarbonyl)-3-bromopropylamine and $Et_3N$ were added and the reaction was stirred for an additional 24 h, then dried *in vacuo*. Next, a slurry of SiliaMetS Dimercaptotriazine beads (392 mg, 239 µmol, 4.6 equiv.) (Silicycle, R79030B, 40-63 µm, 0.61 mmol/g) in DMF (1.55 mL) was added. The reaction was stirred at 50 °C for 2 days, cooled to room temperature and filtered. The filtrate was concentrated *in vacuo*, re-dissolved in EtOAc, washed with 0.1 M $NaHCO_3$ then sat. NaCl. The combined organics were dried over $Na_2SO_4$, filtered and concentrated in vacuo. This material was treated with of 20% TFA (160 µL) in DCM for 40 min at room temperature and concentrated *in vacuo* to yield a yellow residue as c-rucaparib•2TFA (3.2 mg, 61% overall yield). HRMS (ESI+) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{25}N_4OF$, 381.20852; found, 381.20846. $^1H$ NMR (400 MHz, $d_6$-DMSO): δ 7.74 (d, *J* = 8.5, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.53 (dd, *J* = 2.5, 11.0 Hz, 1H), 7.33 (dd, *J* = 2.5, 9.0 Hz, 1H), 3.55 (d, *J* = 5.0 Hz, 2H), 3.17-3.15 (m, 3H), 3.07-3.03 (m, 3H), 2.84 (s, 3H), 2.27-1.95 (m, 4H). $^{13}C$ NMR (100 MHz, $d_6$-DMSO): δ 170.89, 159.39 (d, *J* = 237.0 Hz), 137.32 (d, *J* = 12.0 Hz), 134.64, 133.78, 131.32, 128.3, 124.85 (d, *J* = 9 Hz), 123.35, 118.2, 112.68, 110.19 (d, *J* = 26.0 Hz), 100.97 (d, *J* = 26.0 Hz), 59.47, 52.53, 42.26, 38.46, 36.41, 28.58, 22.25.

**Synthesis of c-Veliparib**




To a 20 mL vial was added veliparib (30 mg, 94.5 µmol, 1.0 equiv.), *N*-(tert-butoxycarbonyl)-3-bromopropylamine (225.2 mg, 945 µmol, 10 equiv.), DIPEA (66 µL, 378 µmol, 4.0 equiv.) in DMF (5 mL). The reaction was stirred at room temperature for 7 days (LC-MS analysis revealed ~35% conversion to desired product) then dried *in vacuo*. Next, the reaction mixture was dissolved in MeCN (10 mL) and transferred to a 100 mL round-bottom flask. To this solution were added SiliaMetS Dimercaptotriazine beads (6.3 g, 3.78 mmol, 40.0 equiv.) (Silicycle, R79030B, 40-63 µm, 0.59 mmol/g). The reaction was stirred at 50 °C for 22 h, then cooled to room temperature and filtered using Celite. The filtrate was concentrated *in vacuo*, re-dissolved in dichloromethane, washed with 0.1 M $NaHCO_3$ then sat. NaCl. The combined organics were dried over $Na_2SO_4$, filtered through Celite and concentrated *in vacuo*. The desired BOC-protected c-veliparib was separated from unreacted veliparib by silica gel chromatography (0-20% gradient MeOH in DCM). Fractions containing BOC-protected c-veliparib were identified by LC-MS analysis, pooled and concentrated in vacuo. This material was treated with 20% TFA in DCM for 40 min at room temperature in the presence of SiliaMetS Thiol beads (33 mg) (Silicycle, R51030B, 40-63 µm, 1.39 mmol/g) as a radical scavenger. After drying *in vacuo*, the product was re-suspended in MeOH, extracted 3x with hexanes, and the MeOH layer was filtered using Celite and the filtrate was concentrated *in vacuo* to yield a clear colorless oily residue as c-veliparib•2TFA (11.5 mg, 29% overall yield). HRMS (ESI+) *m/z*: $[M+Na]^+$ calcd. for $C_{16}H_{23}N_5O$, 324.17948; found, 324.18023. $^1H$ NMR (400 MHz, $CD_3OD$): δ 7.98 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 4.29 (t, *J* = 8.0 Hz, 2H), 3.69 (td, *J* = 8.0, 4 Hz, 2H), 3.1 – 3.0 (m, 2H), 2.66 (s, 3H), 2.55 – 1.7 (m, 10H).

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